

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

## PCT

### WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/GB2005/000496

International filing date (day/month/year)  
11.02.2005

Priority date (day/month/year)  
13.02.2004

International Patent Classification (IPC) or both national classification and IPC  
C07C221.00, C07C225.36

Applicant  
KUDOS PHARMACEUTICALS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA



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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/GB2005/000496

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.  
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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation (Form PCT/ISA206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
  - ☐ paid additional fees under protest.
  - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
  - ☐ the parts relating to claims Nos.

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	3,7,9,11,12
	No: Claims	1,2,4-6,8,10
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations

**see separate sheet**

**Re Item IV**

**Lack of unity of invention**

- D1: US-B1-6 320 063 (DENNY WILLIAM ALEXANDER ET AL) 20 November 2001 (2001-11-20)
- D2: LEE H H ET AL: "A LARGE-SCALE SYNTHESIS OF THE BIOREDUCTIVE DRUG 1,4-BIS(4-(DIMETHYL-AMINO)ETHYL)AMINO-5,8-DIHYDROXYANTHRACENE-9,10-DIONE BIS-N-OXIDE (AQ4N)" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY, LETCHWORTH, GB, no. 19, 1999, pages 2755-2758, XP009049380 ISSN: 0300-922X
- D3: WO 03/078387 A (BTG INTERNATIONAL LIMITED; DENNY, WILLIAM, ALEXANDER; PATTERSON, LAURE) 25 September 2003 (2003-09-25)

1. The present application relates to a process for the preparation of compound AQ4N (2) or a salt or solvate thereof wherein the process includes the oxidation of a compound AQ4 (1) with an oxidising agent at a reaction temperature not exceeding 10°C. A process for the preparation of AQ4N (2) comprising the conversion of p-hydroquinone (4) and 3,6-difluorophthalic anhydride (DFPA, 5) into 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) in a stirrable solvent at a temperature not exceeding 200°C is claimed as well. A process for the preparation of AQ4N(2) including the conversion of 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) into AQ4(1) wherein the reaction solution in which the conversion takes place is treated with an ammonium hydroxide and brine solution cooled to 0°C is also claimed.
2. The present application does not fulfil the requirement of unity of invention (Rule 13.1 PCT). The reason therefore is that the application relates to three different inventions, namely:

1. Claims 1-7

Process for the preparation of compound AQ4N (2) or a salt or solvate thereof wherein the process includes the oxidation of a compound AQ4 (1) with an oxidising agent at a reaction temperature not exceeding 10°C.

2. Claims 8-11

Process for the preparation of AQ4N (2) comprising the conversion of p-hydroquinone (4) and 3,6-difluorophthalic anhydride (DFPA, 5) into 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) in a stirrable solvent at a temperature not exceeding 200 °C.

3. Claim 12

Process for the preparation of AQ4N(2) including the conversion of 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) into AQ4(1) wherein the reaction solution in which the conversion takes place is treated with an ammonium hydroxide and brine solution cooled to 0 °C.

3. There is no common technical feature linking the three inventions which is novel and inventive over the prior art taking into account that compounds AQ4N (2), AQ4 (1), p-hydroquinone (4), 3,6-difluorophthalic anhydride (DFPA, 5) and 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) are known in the art (D1-D3). Hence, the application is not unitarian.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

First invention

1. Claims 1-7 relate to a process for the preparation of compound AQ4N (2) or a salt or solvate thereof wherein the process includes the oxidation of a compound AQ4 (1) with an oxidising agent at a reaction temperature not exceeding 10 °C.
2. D1 discloses the preparation of AQ4N (2) by oxidation of a compound AQ4 (1) with the Davis reagent (an oxaziridine) wherein the reaction takes places at 20 °C.
3. D2 discloses the preparation of AQ4N (2) by oxidation of a compound AQ4 (1) with the

Davis reagent (an oxaziridine) wherein the reaction takes places at 0 °C.

4. D3 discloses the preparation of salts of AQ4N by treatment of AQ4N with an acid.

Novelty

5. The subject-matter of claims 1, 2 and 4-6 is not novel in the sense of Art. 33(2) PCT. D2 discloses the preparation of AQ4N (2) and the di HCl derivative thereof by oxidation of a compound AQ4 (1) with an oxidising agent, an oxaziridine, at 0 °C (see paragraph 3 above) using dichloromethane as a solvent. This disclosure anticipates the subject-matter of claims 1, 2 and 4-6, which is therefore not novel.

Inventive step

6. Dependent claims 3 and 7 do not contain any feature which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

Second invention

1. Claims 8-11 relate to a process for the preparation of AQ4N (2) comprising the conversion of p-hydroquinone (4) and 3,6-difluorophthalic anhydride (DFPA, 5) into 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) in a stirrable solvent at a temperature not exceeding 200 °C.
2. D1 and D2 disclose the preparation of AQ4N (2) comprising the conversion of p-hydroquinone (4) and 3,6-difluorophthalic anhydride (DFPA, 5) into 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) in a stirrable solvent at a temperature (200+5) °C/(200-5) °C (see column 10 in D1 and page 2757 in D2).

Novelty

3. The subject-matter of claims 8 and 10 is not novel in the sense of Art. 33(2) PCT. D1 and D2 disclose the preparation of AQ4N (2) comprising the conversion of p-

hydroquinone (4) and 3,6-difluorophthalic anhydride (DFPA, 5) into 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) in a stirrable solvent at a temperature (200+5)°C/(200-5)°C wherein the end product is treated by slurring with ice and concentrated HCl. These disclosures anticipate the subject-matter of the above-mentioned claims which is therefore not novel.

**Inventive step**

4. Dependent claims 9 and 11 do not contain any feature which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

**Third invention**

1. Claim 12 relates to a process for the preparation of AQ4N(2) including the conversion of 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) into AQ4(1) wherein the reaction solution in which the conversion takes place is treated with an ammonium hydroxide and brine solution cooled to 0°C.
2. D1 and D2 disclose the conversion of 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) into AQ4(1) wherein the reaction solution is treated with brine and the precipitate is collected by filtration and washed with an ammonium hydroxide (see columns 10 and 11 in D1 and page 2757 in D2).

**Novelty**

3. The subject-matter of claim 12 is novel in the sense of Art. 33(2) PCT. None of the available documents of the prior art discloses a process for the preparation of AQ4N(2) including the conversion of 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) into AQ4(1) wherein the reaction solution in which the conversion takes place is treated with an ammonium hydroxide and brine solution cooled to 0°C (see paragraph 2).

**Inventive step**

4. The subject-matter of claim 12 cannot be considered to involve an inventive step in the sense of Art. 33(3) PCT.
- 4.1. D1 and D2 disclose the conversion of 1,4-difluoro-5,8-dihydroxyanthracene (DDA, 6) into AQ4(1) wherein the reaction solution is treated with brine and the precipitate is collected by filtration and washed with an ammonium hydroxide (see columns 10 and 11 in D1 and page 2757 in D2).
- 4.2. The problem to be solved in the application can be seen in the provision of an alternative process.
- 4.3. The solution proposed in the application is the treatment of the reaction solution with an ammonium hydroxide and brine solution cooled to 0°C instead of treatment with brine in a first step and with ammonium hydroxide in a second step. However, this is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. An inventive step could only be acknowledged if comparative examples with D1/D2 would have been provided showing that this selection leads to unexpected effects (a better result than in D1/D2). As such an evidence is not available at the moment, an inventive step cannot be acknowledged.

Further comments

5. It is clear from the description on pages 5-7 and the examples that the following features are essential to the definition of the invention:
  - (1) the oxidising agent used in the process (not any single one can be used with good results),
  - (2) the temperature of addition of the oxidant to the reaction mixture,
  - (3) the preparation of the salts of AQ4N.

Since independent claim 1 does not contain these features, it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition



of the invention.

6. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims.
7. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 19(2) and 34(2) b) PCT, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.